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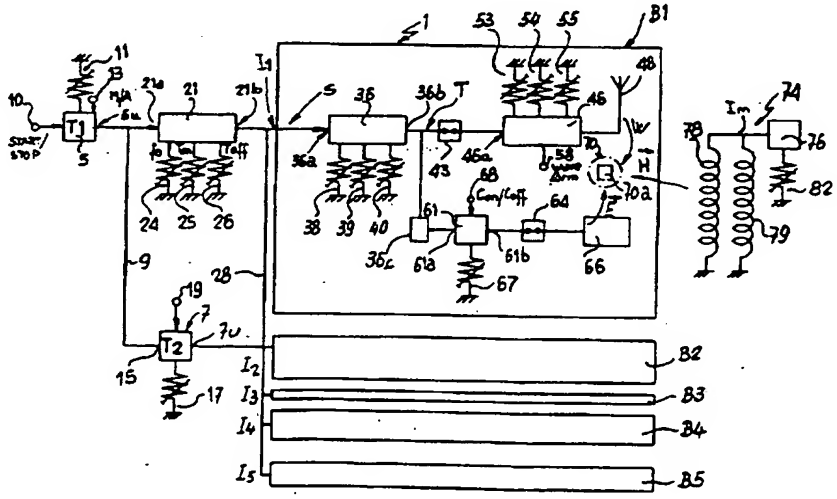

(57) Abstract

Device for the modulation of biological functions, comprising, according to the invention: means of generating an electromagnetic field (46) capable of producing, when activated, a radiofrequency signal (W) which can be directed towards an application area (70), and/or means of generating an electrical field (61), capable of applying, when activated, an electrical field (E) to the said application area (70), and/or means of generating a magnetic field (74), capable of applying, when activated, a magnetic field (H) to the said application area (70), and/or means of generating radiation at optical frequencies, capable of directing, when activated, the said radiation on to the said application area, and/or means of generating electromagnetic sound waves, capable of directing, when activated, the said waves on to the said application area.

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# DEVICE AND PROCESS FOR THE MODULATION OF THE BIOLOGICAL FUNCTIONS OF BIOLOGICAL STRUCTURES

The present invention relates to a device and process for the modulation of the biological functions of biological structures.

The study of the interactions between electromagnetic fields and biological structures has become an extremely fruitful field of research, although phenomena of interference have been observed empirically in various civilizations from antiquity onwards.

There is now ample experimental evidence of the possibility of controlling certain functions of biological structures by the application of electromagnetic fields. For example, the application of electromagnetic fields to accelerate bone regeneration is known, with particular reference to fractures with delayed spontaneous healing.

The thermal effects of electromagnetic fields on biological structures are also widely known; these thermal effects are obtained by directing high-power and high-frequency electromagnetic fields at biological structures, and involve an increase in molecular vibration, with a consequent increase in the entropy of the biological structures.

The object of the present invention is to provide a device and process for applying magnetic and/or electrical and/or electromagnetic fields and/or optical-frequency radiation and/or electromagnetic sound waves to biological structures, thereby producing effects of modulation of the biological functions.

The above object is achieved by the present invention in that it relates to a device and process of the type described in Claims 1 and 20 respectively for the treatment of biological structures.

The invention will now be illustrated with reference to the attached drawings which show a non-restrictive preferred embodiment in which:

- Figure 1 shows schematically the simplified electrical circuit of a device for the treatment of biological structures, constructed according to the specifications of the present invention;
- Figure 2 is a logical diagram of the operation of the device shown in Figure 1;
- Figure 3 shows the variation in time of some signals of the device shown in Figure 1; and
- Figure 4 shows, by means of an electrical circuit diagram, the principle of operation of a biological reaction.

With reference to Fig. 1, the number 1 indicates as a whole a device for the treatment of biological structures according to the invention. The device 1 comprises a first timer 5 and a second timer 7 connected to the timer 5 through a control line 9. The first timer 5 is provided with a control input 10 (START/STOP) and a device 11 for manual regulation of the time-delay period T1 which can be provided by the timer 5. The first timer 5 is also provided with an input 13 which can switch between automatic and manual operating modes of the timer 5; in the automatic operating mode, the output 5u of the timer 5 has a first logical value, for example a logical "1", for a time T1 from the activation (START) of the control input 10, while in the manual operating mode the output 5u maintains the first logical value "1" between two successive activations (START/STOP) of the control input 10.

The second timer 7 is provided with a control input 15 (START/STOP) connected to the line 9 and with a device 17 for the manual regulation of the time-delay period T2 provided by the timer 7. The second timer 7 is also provided with an input 19 which can switch between automatic and manual operating modes of the timer 7; in the automatic operating mode, the output 7u of the timer 7 has a first logical value, for example a logical "1", for a time T2 from the activation (START) of the control input 15, while in the manual operating

mode the output 7u maintains the first logical value between two successive activations (START/STOP) of the control input 15.

The output 5u of the first timer 5 communicates with a control input 21a of a bistable circuit 21 which can generate a square-wave signal S at one of its outputs 21b when a logical "1" is applied to the input 21a. In particular, the circuit 21 is provided with three regulating devices 24, 25 and 26 which can, respectively, set the frequency fo of the signal S, the amplitude of the period (Ton) in which the signal S has a logical value of "1" and the amplitude of the period (Toff) in which the signal S has a value equal to a logical "0".

The output 21b of the circuit 21 is connected to a control line 28 communicating with the inputs I1, I2, I3, I4, I5 of corresponding generator units B1, B2, B3, B4 and B5. The structures of the units B1 - B5 are completely identical, and consequently, for the sake of simplicity, only the unit B1 will be described and illustrated.

The unit B1 comprises a bistable circuit 36 having a control input 36a communicating with the control line 28. The bistable circuit 36 can generate a square-wave signal T, with a frequency and duty cycle which can be regulated, when a logical "1" is applied to the input 36a. In particular, the circuit 36 is provided with three regulating devices 38, 39 and 40 which can, respectively, set the frequency fo of the signal T, the amplitude of the period (Ton) in which the signal T has a logical value of "1" and the amplitude of the period (Toff) in which the signal T has a value equal to a logical "0".

The output 36b of the circuit 36 communicates, through an interposed switch 43, with a control input 46a of a transmitter 46 which can generate a radiofrequency signal W at the output on an antenna 48. The antenna 48 may be of the rod, wire or parabolic

type with the possibility of automatic aiming of the antenna 48.

In particular, the signal W is generated when a signal equivalent to a logical "1" is applied to the input 46a. The circuit 46 is provided with three regulating devices 53, 54 and 55 which can, respectively, select the frequency fo of the signal W, the amplitude of the period (Ton) in which the signal W has a "high" value and the amplitude of the period (Toff) in which the signal has a "low" value. The circuit 46 is also provided with a control device 58 for the selection of the type of wave form (SQUARE, TRIANGULAR, SINUSOIDAL WAVE, etc.) of the radiofrequency signal W. The signal W may also have, for example, a power which can be regulated from 0.1 to 500 watts and a frequency which can be regulated from 1 Hz to 1 terahertz. For applications using electromagnetic sound waves, a receiver-converter device (not illustrated) is provided to receive the radiofrequency signal W and convert it to a sound signal. In this case, a signal amplifier may be provided at the output of the receiver-converter. Alternatively, a sound transmitter may be used. The sound signal lies in an audible or inaudible frequency range.

Similarly, for applications using optical-frequency radiation, a receiver-converter device (not illustrated) is provided to receive the radiofrequency signal and convert it into a light signal in a predetermined frequency range.

The unit B1 also comprises a static power supply circuit 61 which has a control unit 61a communicating with the output 36b through a relay 36c electrically connected to a 220 V alternating current line, and an output 61b communicating, through an interposed switch 64, with at least one metal sheet, for example a rectangular plate 66. The said plate is made, for example, from platinum, gold, copper, aluminium, zinc,

carbon or metal alloy, or from a core, of gold for example, covered by a coating, of copper for example.

The circuit 61 can generate at the output, when there is a logical "1" signal at the input, a constant voltage Vplate (lying for example between 10 and 200,000 volts) whose value can be regulated manually by means of a device 67. The circuit 61 can also set its output 61b to a voltage of zero when a logical "0" is present at the input 61a.

The circuit 61 is also provided with an input 68 for the selection of the rise mode of the voltage Vplate; in a first operating mode (Cond-ON), the voltage Vplate (of the rectangular pulse type with an amplitude proportional to the width of the period Ton) rises in a ramp with a slope which can be regulated, while in a second operating mode (Cond-off) the voltage Vplate rises in steps.

The voltage Vplate applied to the plate 66 can generate an electrical field E directed towards an application area 70 to which the radiofrequency signal W is also sent.

The device 1 also comprises a magnetic field generator 74 comprising a power supply circuit 76 and one or more coils, for example two, indicated by 78 and 79, supplied from the circuit 76. The circuit 76 can supply to the coils 78, 79 a current Im having a predetermined wave form (for example rectangular, sinusoidal, triangular, etc.) and an intensity which can be regulated by means of a device 82. The coils 78, 79 can generate a magnetic field H directed towards the application area 70. The magnetic field H may have an intensity of, for example, between 1 and 30,000 gauss and may be continuous or pulsed with a frequency of between 0.1 Hz and 1 kHz.

The operation of the device 1 will now be described, with particular reference to Figure 2.

Initially (block 100) the user selects (by acting on the input 10) an operating mode of the manual or automatic type. If the manual mode is selected, the

block 100 is followed by a block 110; otherwise (with automatic mode selected) the block 100 is followed by a block 120. The block 120 starts the timer 5 which sets its output to a voltage level equal to a logical "1". The block 120 is followed by a block 125 in which the circuit 21 is switched on to produce at the output the square-wave logic signal S having a frequency fo and a duty cycle which can be regulated by means of the devices 24, 25 and 26. Figure 3 shows, purely by way of example and without restriction, the logical state of the output 5u after a start of the device and the corresponding variation with time of the logic signal S.

The signal S is then sent to the circuit 36 which generates a square-wave logic signal T at its output 36b for all the time intervals in which the signal S has the value "1". The output 36b of the circuit 36 has a logical value of "0" for all the instants in which the signal S is equal to a logical "0".

The signal T is thus sent by the 12 V d.c. line to the transmitter 46 and, through the relay 36c, by the 220 V a.c. line, for example, to the circuit 61; in particular, the transmitter 46 emits through the antenna 48 a pulse train having a wave form, frequency and duty cycle which can be regulated, for all the time intervals for which the signal T has the value "1". The transmitter 46 does not emit any signal for all the instants in which the signal T is equal to a logical "0".

The circuit 61 also supplies the plate 66 which produces the field E, for all the time intervals in which the signal T is equal to "1". The circuit 61 does not supply the plate 66 in all instants in which the signal T is equal to a logical "0".

The block 125 is followed by a block 130 which at the end of the time T1 is followed by a block 140 by means of which the user selects a manual or automatic operating mode for the second timer 7, by acting on the input 19. If the manual mode is selected, the block 140

is followed by a block 150; otherwise (with automatic mode selected) the block 140 is followed by a block 160. The block 160 starts the timer 7 which sets its output 7u to a voltage level equal to a logical "1". The block 160 is followed by a block 165 in which the circuit 36 is switched on and produces a square-wave logic signal T at its output.

The signal T is thus sent to the transmitter 46 and, through the relay 36c, to the circuit 61; in particular, the transmitter 46 emits through the antenna 48 a pulse train having a wave form, frequency and duty cycle which can be regulated, for all the time intervals for which the signal T has the value "1". The transmitter 46 does not emit any signal for all the instants in which the signal T is equal to a logical "0".

The circuit 61 also supplies the plate 66 which produces the field E, for all the time intervals in which the signal T is equal to "1". The circuit 61 does not supply the plate 66 for all the instants in which the signal T is equal to a logical "0".

The block 165 is followed by a block 170 which at the end of the time T2 stops the operation of the device 1. The circuit 46 is provided with a manual control for the transmission of the signal in continuous mode, also stopping operation after the block 170.

The block 110, in a similar way to block 125, switches on the circuit 21 which in turn controls the circuit 36 driving the transmitter 46 and the circuit 61. The operations executed by the block 110 terminate (block 111) following a new activation (STOP) of the control input 10.

The block 150, in a similar way to block 165, switches on the circuit 36 which drives the transmitter 46 and the circuit 61. The operations executed by the block 150 terminate (block 151) following a new activation (STOP) of the control input 19.

In operation, a biological structure 70a to be treated is placed in the application area 70; this biological structure 70a may consist of a group of cells contained in a container (in vitro treatment) or may be a part of the body of a living organism (in vivo treatment).

When necessary, optical-frequency radiation and/or electromagnetic sound waves are applied by directing the radiation and/or waves preferentially towards the receptor organs present in the biological structure.

The type of effect which may be obtained on the biological structures depends on the type of cells used in the treatment and on the intensity, the orientation and the frequency of the electrical and/or magnetic and/or electromagnetic fields and/or of the optical-frequency radiation and/or electromagnetic sound waves used.

The electrical field E and the magnetic field H are, for example, disposed with versors of propagation parallel to each other and the electromagnetic field W is normally transverse with respect to the magnetic and electrical field.

One observed effect of the action of one or more of the three fields and/or of the optical-frequency radiation and/or electromagnetic sound waves, in suitable conditions, is the induction of cellular necrosis.

In particular, it has been observed that in these conditions it is possible to produce cellular necrosis in a selective way, and therefore:

- by exposing various lines of normal cells to the treatment, to obtain the effect in question on predetermined lines; and
- by exposing normal and neoplastic cells to the treatment, to obtain the effect, for example, only on the pathological cells or vice versa.

The process of necrosis has been produced in vitro with an electromagnetic field W having a frequency within the range 1 Hz - 50 MHz, a power up to 60 watts

and a wave form of the sinusoidal or square type. A voltage of the order of 200-380 volts is applied to the plate 66 and the magnetic field used has an intensity of up to 40 gauss and is of the pulsed or continuous type.

The process of necrosis indicated above has been produced in vivo with an electromagnetic field W having a frequency within the range 1 Hz - 8 MHz, a power up to 60 watts and a wave form of the sinusoidal or square type. A voltage of the order of 100-380 volts is applied to the plate 66 and the magnetic field used has an intensity of up to 40 gauss and is of the pulsed or continuous type.

It is hypothesized that the biological mechanism producing the cellular necrosis is based on an effect of the said signals on the energy metabolism of the cell. More precisely, it is suggested that the chromosomes, after signals have been received as a result of the variation of potential of the cytoplasm membrane, cause genes, by an electromechanical effect, to emit signals which regulate the cell dynamics for normal cell functions and for mitochondrial activity for the production of ATP.

The production of ATP is therefore considered to be regulated by signals which, originating from the genes, act on specific glycoprotein structures of the mitochondrial membrane.

A model of the operation of the mitochondrion is assumed to be provided by the circuit in Figure 4, in which the Zener diode $D_z$ (of the frequency type) represents the on-off operation as a function of the frequency, the impedance Z represents the impedance of the glycoprotein sensors present in the mitochondrial membrane, and the transistor represents the ATP activation process.

The means used are considered to cause cellular necrosis by producing the elongation of the carbohydrate chains of the mitochondrial glycoprotein sensors with a consequent increase in their impedance

and therefore a decrease in ATP production. It is therefore the decreased availability of ATP which is believed to result, beyond a certain threshold, in cell necrosis.

It has also been hypothesized that superconducting junctions of the Josephson type are formed between adjacent cells during the aforesaid process of necrosis. The Josephson effect, discovered in 1962, is found when two superconductors are brought close enough together that they are separated only by a thin dielectric layer (Josephson junction). The presence of such regions between adjacent cells has not yet been demonstrated, but it may be supposed that the currents of positive ions which pass through the cell membranes and are propagated along the cellular structure may be considered to be "supercurrents".

In addition to the regulation of mitochondrial ATP production described above, it is believed that other functions and organelles of the cell may also be controlled, as a result of specific variations of the membrane potential, by the genome through activation by physical signals and target glycoprotein structures.

It is clear from the above description that the device 1, by virtue of the action of one or more of the three fields E, H and W, and/or of optical-frequency radiation and/or electromagnetic sound waves mentioned above, is capable of producing effects of modulation on the biological functions of biological structures.

The device 1 may advantageously be used to modulate molecular activity during biological and biochemical reactions and interactions.

In particular, the process of necrosis described above may advantageously be used to control (and reduce) the growth and reproduction of pathological cells, for example neoplastic cells; alternatively it is possible to accelerate the process of regeneration of normal cells, for example by rapid scar formation at surgical incisions.

CLAIMS

1. Device for the modulation of biological functions, characterized in that it comprises:

- means of generating an electromagnetic field (46) capable of producing, when activated, a radiofrequency signal (W) which can be directed towards an application area (70), and/or
- means of generating an electrical field (61), capable of applying, when activated, an electrical field (E) to the said application area (70), and/or
- means of generating a magnetic field (74), capable of applying, when activated, a magnetic field (H) to the said application area (70), and/or
- means of generating radiation at optical frequencies, capable of directing, when activated, the said radiation on to the said application area, and/or
- means of generating electromagnetic sound waves, capable of directing, when activated, the said waves on to the said application area.

2. Device according to Claim 1, characterized in that it comprises first control means (36) capable of controlling the said means of generating an electromagnetic field (46) and the said means of generating an electrical field (61) by means of a first control signal (T) generated by the said first control means (36) when these are active; the said first control signal (T) comprising cycles of activation (Ton) of the said means of generating an electrical field (61) and the said means of generating an electromagnetic field (46), alternating with cycles of inhibition (Toff) in which the said means of generating an electrical field (61) and the said means of generating an electromagnetic field (46) are kept inactive.

3. Device according to Claim 2, characterized in that it comprises second control means (21) capable of generating, when active, a second control signal (S) for the said first control means (36); the said second

control signal comprising cycles of activation (Ton) of the said first control means, alternating with cycles of inhibition (Toff) in which the said first control means (36) are kept inactive.

4. Device according to Claim 3, characterized in that it comprises first timer means (5) interacting with the said second control means (21); the said first timer means (5) being capable of activating, following a start signal, the said second control means (21) for a first timing interval whose duration (T1) can be regulated by regulation means (11) associated with the first timer means (5).

5. Device according to Claim 3, characterized in that it comprises first timer means (5) interacting with the said second control means (21); the said first timer means (5) being capable of activating the said second control means (21) for a first timing interval whose duration extends between two successive operations (START/STOP) of activation means (10) associated with the said first timer means.

6. Device according to Claim 4 or 5, characterized in that it comprises second timer means (7) interacting with the said first control means (36); the said second timer means (7) being capable of activating the said first control means (36) for a second timing interval (T2) whose duration can be regulated by regulation means (17) associated with the said second timer means (7).

7. Device according to Claim 4 or 5, characterized in that it comprises second timer means (7) capable of activating the said first control means (36) for a second timing interval whose duration extends between two successive operations (START/STOP) of activation means (19) associated with the said timer means.

8. Device according to Claim 6 or 7, characterized in that the said second timer means (7) communicate with the said first timer means (5) and can be activated by the said first timer means (5) at the end of the said first timing interval (T1).

9. Device according to any one of the preceding claims, characterized in that the said means of generating an electromagnetic field (46) comprise transmitter means (46) interacting with antenna means (48); the said transmitter means (46) being provided with regulating means (53, 54, 55) for the selection of the frequency of the electromagnetic signal emitted.

10. Device according to any one of the preceding claims, characterized in that the said means of generating an electromagnetic field (46) comprise transmitter means provided with regulating means (58) for the selection of the wave form of the electromagnetic signal emitted.

11. Device according to any one of claims 2 to 10, characterized in that the said means of generating an electrical field (61) comprise electrical power supply means (61) which can be activated by the said first control means (36) and which can supply a voltage to plate means (66) for the generation of the said electrical field (E).

12. Device according to any one of the preceding claims, characterized in that the said means of generating an electrical field (61) comprise electrical power supply means (61) which can be activated by the said first control means (36) and which can supply plate means (66) with rectangular voltage pulses whose width can be regulated as a function of the said activation cycle of the first control signal (T); the said means of generating an electrical field (61) interacting with regulating means (67) capable of regulating the slope of the said rectangular pulses.

13. Device according to any one of Claims 2 to 13, characterized in that the said first control means (36) interact with regulating means (38, 39, 40) capable of selecting the amplitude of the said activation cycles (Ton), the amplitude of the said inhibition cycles (Toff) and the frequency of the said first control signal (T).

14. Device according to any one of Claims 3 to 13, characterized in that the said second control means (21) interact with regulating means (24, 25, 26) to regulate the amplitude of the said activation cycles (Ton), the amplitude of the said inhibition cycles (Toff) and the frequency of the said second control signal (S).

15. Device according to any one of the preceding claims, characterized in that the said means of generating a magnetic field (74) comprise current supply means (76) and coil means (78, 79) interacting with the said current supply means (76); the said means of generating a magnetic field (74) also comprising selection means (82) capable of regulating the wave form and intensity of the current supplied to the said coil means (78, 79).

16. Device according to any one of the preceding claims, characterized in that the said means of generating an electromagnetic field (W) generate a field having a frequency within the range from 0.1 Hz - 100 GHz, advantageously from 1 Hz to 100 MHz, a power of up to 1000 watts, and advantageously up to 60 watts, and a wave form of the sinusoidal/triangular/square type; the said means of generating an electrical field (61) being capable of applying to plate means (66) a voltage of the order of 10 - 200,000 volts, and advantageously of the order of 200-380 volts; the said means of generating a magnetic field (74) generating a field with an intensity of up to 30,000 gauss, and advantageously up to 40 gauss.

17. Device according to any one of the preceding claims, characterized in that the said means of generating an electromagnetic field generate a field (W) having a frequency within the range from 1 Hz - 8 MHz, a power of up to 60 watts, and a wave form of the sinusoidal/triangular/square type; the said means of generating an electrical field (61) being capable of applying to plate means (66) a voltage of the order of 100-380 volts; the said means of generating a magnetic

field (74) generating a field with an intensity of up to 40 gauss.

18. Device according to Claim 1, characterized in that the said means of generating optical-frequency radiation comprise means of receiving and converting the said radiofrequency signal (W) into an optical-frequency signal applied in the said application area.

19. Device according to Claim 1, characterized in that the said means of generating electromagnetic sound waves comprise means of receiving and converting the said radiofrequency signal (W) into an electromagnetic sound wave signal applied in the said application area.

20. Process for the modulation of the biological functions of biological structures, characterized in that it comprises the phases of:

- disposing a biological structure (70a) to be treated in an application area;
- generating an electromagnetic field (W) to direct this electromagnetic field (W) towards the said application area (70), and/or
- generating an electrical field (E) to apply the said electrical field (E) to the said application area (70), and/or
- generating a magnetic field (74) and applying this magnetic field (H) in the said application area (70), and/or
- generating optical-frequency radiation and directing it towards the said application area, and/or
- generating electromagnetic sound waves and directing them towards the said application area.

21. Process according to Claim 20, characterized in that it comprises a first generation phase, in which activation cycles (Ton) are alternated with inhibition cycles (Toff), the said activation cycles comprising the phases of:

- generating an electromagnetic field (W) to direct this electromagnetic field (W) towards the said application area (70), and/or

- generating an electrical field (E) to apply the said electrical field (E) to the said application area (70), and/or
- generating a magnetic field (74) and applying this magnetic field (H) in the said application area (70), and/or
- generating optical-frequency radiation and directing it towards the said application area, and/or
- generating electromagnetic sound waves and directing them towards the said application area.

22. Process according to Claim 21, characterized in that the said inhibition cycles (Toff) comprise at least the phase of generating the said magnetic field (74) and applying this magnetic field (H) in the said application area (70).

23. Process according to Claim 21, characterized in that it comprises a preliminary generation phase comprising first activation cycles (Ton) in which the said first generation phase is made possible, and inhibition cycles (Toff) in which the said phase of preliminary generation is inhibited.

24. Process according to Claim 23, characterized in that the said preliminary generation phase has a predetermined duration (T1) which can be regulated.

25. Process according to Claim 21 or 23, characterized in that the said preliminary generation phase is followed by a first generation phase.

26. Process according to Claim 20, characterized in that the said phase of generating an electromagnetic field (W) comprises the phase of generating an electromagnetic signal with a frequency of between 1 Hz and 1 terahertz and a power of up to 1000 watts.

27. Process according to Claim 20, characterized in that the said phase of generating an electrical field (E) comprises the phase of applying to plate means (66) a voltage of between 10 volts and 200 kilovolts.

28. Process according to Claim 20, characterized in that the said phase of generating a magnetic field (H)

comprises the phase of generating a magnetic field with an intensity of up to 30,000 gauss.

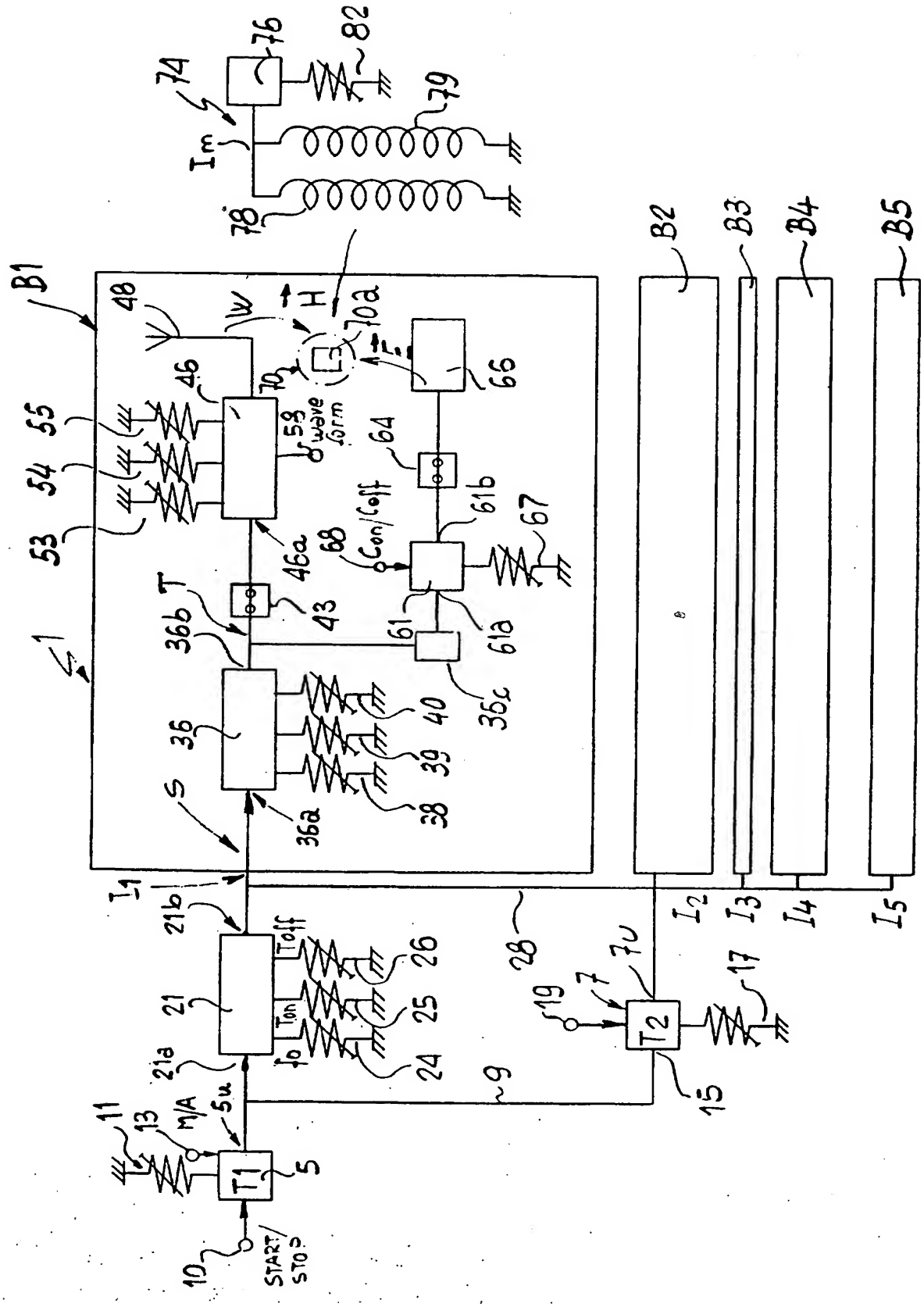


Fig. 1

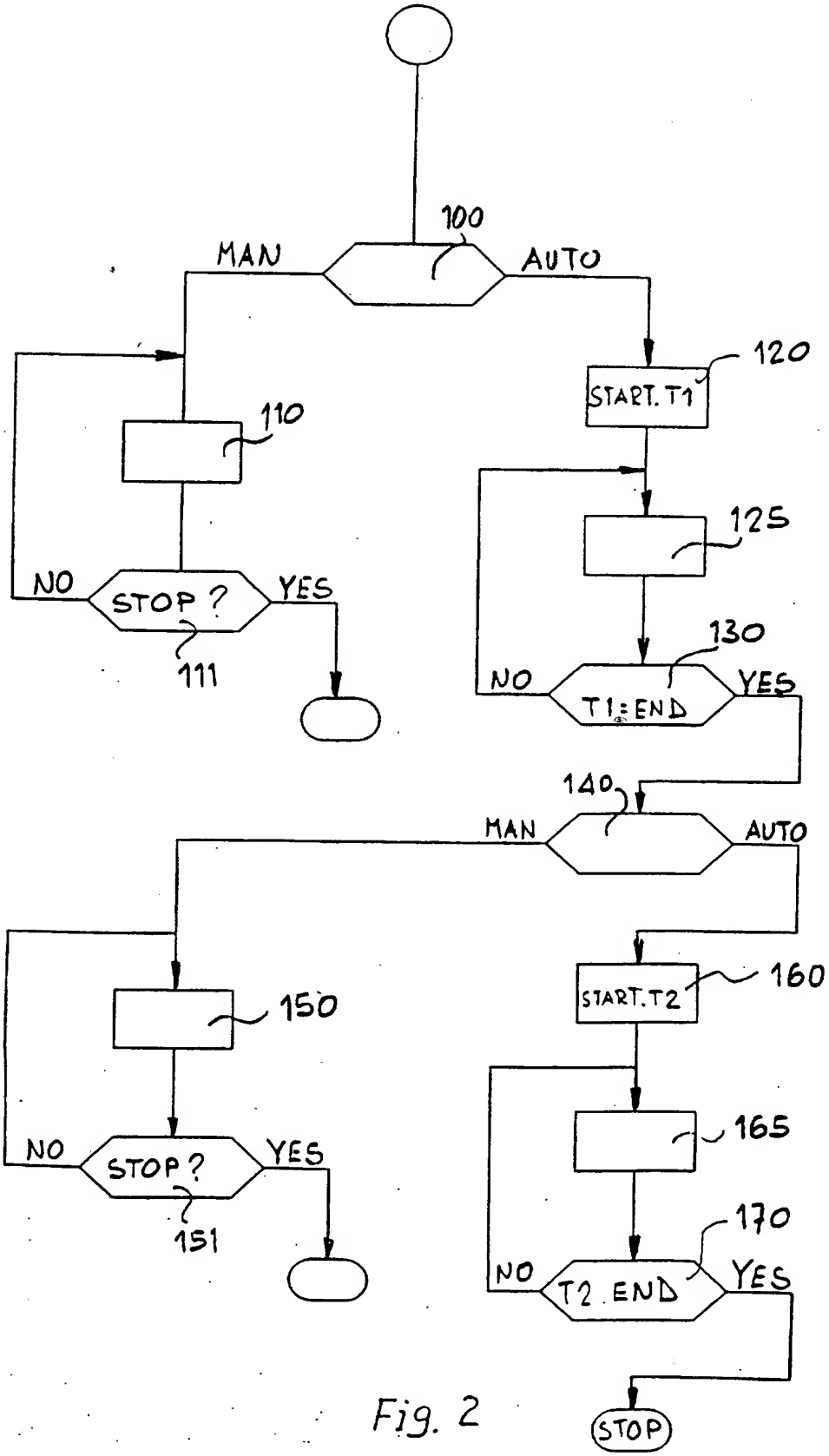


Fig. 2

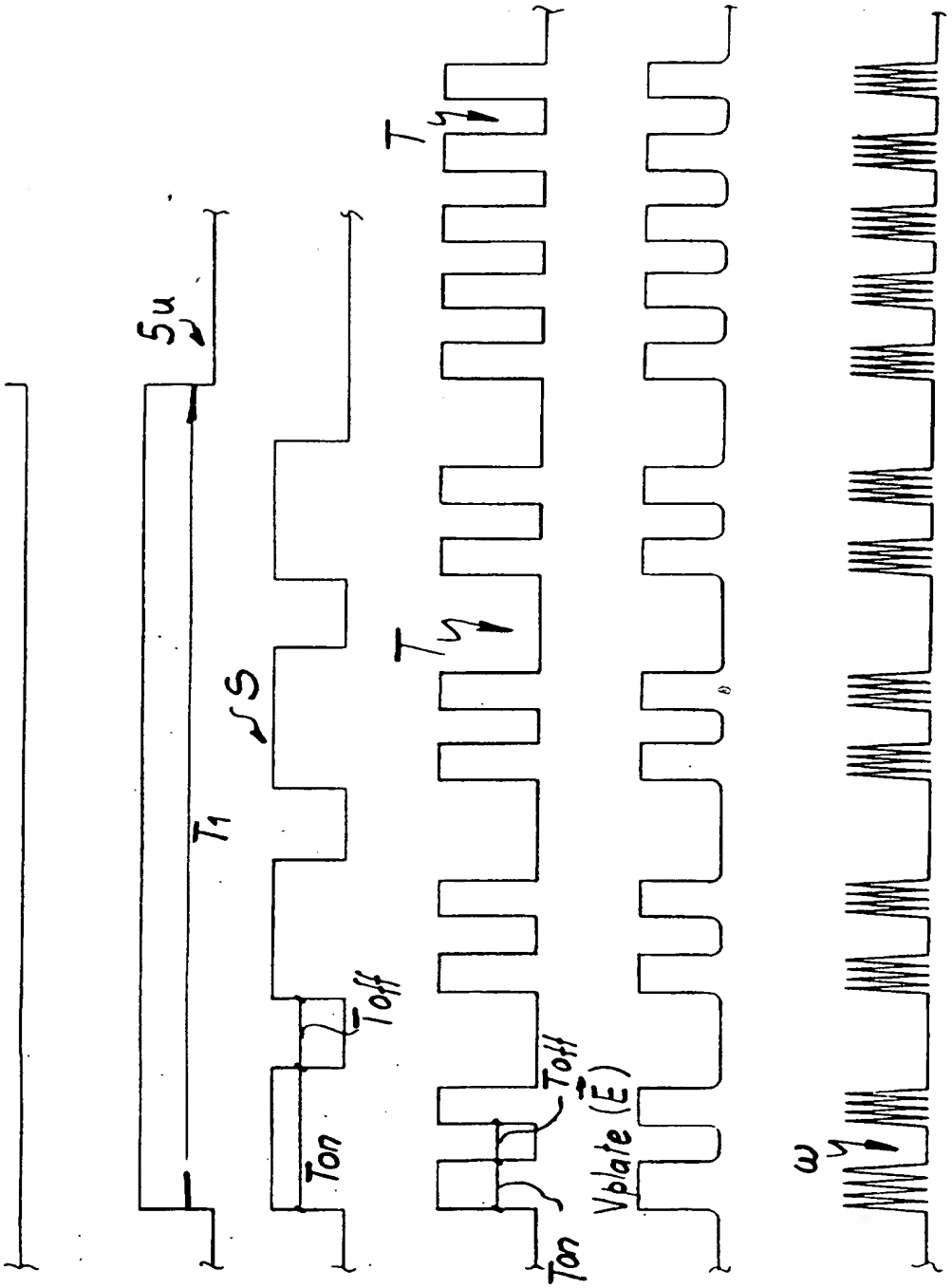


Fig. 3

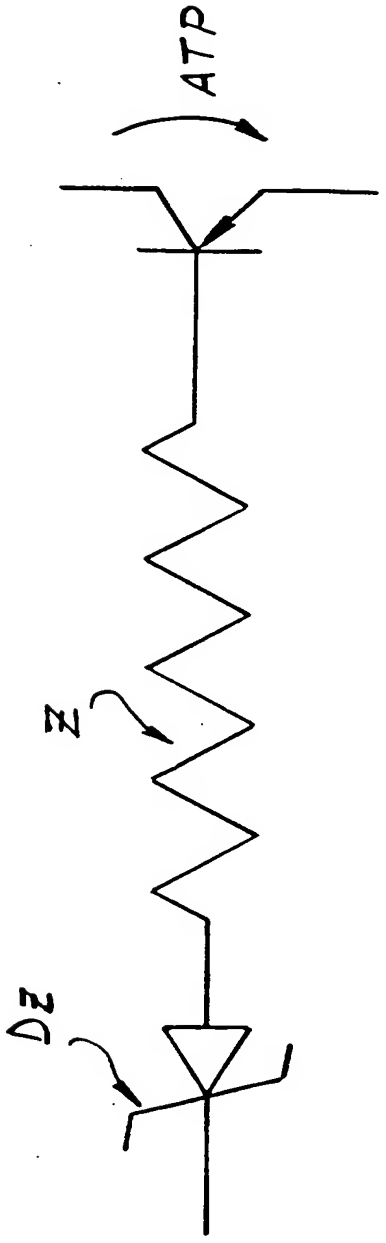


Fig. 4

# INTERNATIONAL SEARCH REPORT

International Application No
PC./EP 96/04197

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US,A,5 186 171 (KUHRY) 16 February 1993<br>see abstract | 1,20 |
| A | WO,A,89 07468 (FELLNER) 24 August 1989<br>see abstract | 1,20 |
| P,A | WO,A,95 33514 (MAGNETIC RESONANCE THERAPEUTICS) 14 December 1995<br>see claim 1 | 1,20 |
| A | WO,A,95 07729 (THETA ELECTRONICS) 23 March 1995<br>see abstract | 1 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 6 February 1997 | 28.02.97 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax ( + 31-70) 340-3016 | Taccoen, J-F |

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# INTERNATIONAL SEARCH REPORT

formation on patent family members

International Application No
PC., EP 96/04197

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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| WO-A-9507729 | 23-03-95 | AU-A- | 7655894 | 03-04-95 |
| | | EP-A- | 0669843 | 06-09-95 |